Beneath the goosebumps

Epidermal stem cells are located in the hair follicle bulge, which maintains contact with arrector pili muscles (APM) throughout the hair cycle. Fujiwara and colleagues hypothesized that bulge–APM interactions may involve epidermal basement membrane players. Indeed, the composition of the bulge extracellular matrix creates a specialized niche not only for bulge stem cells but also for adjacent mesenchymal cells. This specialized basement membrane contains nephronectin, a protein that is upregulated in bulge stem cells and induces APM differentiation and anchorage to the bulge. Deletion of either nephronectin or α8 integrin, a component of the α8β1 integrin nephronectin receptor, resulted in mislocalization of the APM insertion site. Furthermore, nephronectin is a direct target of Wnt/β-catenin signaling. Bulge stem cells therefore appear to function as tendon cells to provide a physical connection for the APM. These results indicate that the heterogeneity of basement-membrane composition is important in tissue patterning. (*Cell* 144:577–89, 2011) *Selected by M. Herlyn*

Following the atopic march

A previous survey of the Tasmanian Longitudinal Health Study, which followed a cohort from age 7 to 44, revealed that childhood eczema and allergic rhinitis predict subsequent asthma. In a continuation of this work, Martin and colleagues found that childhood eczema, especially in conjunction with childhood rhinitis, is strongly associated with current atopic asthma in middle age. Childhood eczema and rhinitis are also associated with childhood asthma that persists as atopic asthma in middle age, as well as atopic asthma that had remitted by middle age. Rhinitis alone predicted the persistence of childhood asthma, and eczema strongly predicted new-onset atopic asthma in middle age. These results are the first to demonstrate the atopic march in adulthood by classifying adult asthma as either atopic or nonatopic. The findings support efforts to prevent eczema and rhinitis in childhood in order to prevent asthma in adult life because increased asthma-associated mortality is observed in individuals over age 60. (*J Allergy Clin Immunol* 127:1473–9, 2011) *Selected by H. Williams*

Double inhibition

Because melanoma is a tumor of transformed melanocytes, which arise from the embryonic neural crest, White and colleagues investigated the relationship between transcriptional programs during neural crest development and *BRAF(V600E)* mutations, which are common in human melanoma. Following identification of enriched neural crest markers, such as crestin, in zebrafish with *BRAF* mutations, a small-molecule screen of more than 200,000 chemicals identified NSC210627 as a compound that inhibited the *crestin*$^+$ lineage during zebrafish embryogenesis. The similar small molecule leflunomide also inhibited dihydro-orotate dehydrogenase (DHODH), led to abrogation of neural crest development in zebrafish, and severely reduced self-renewal of mammalian stem cells. DHODH inhibition modulates transcriptional elongation of genes required for both neural crest development and human melanoma. In addition, a combination of leflunomide and the BRAF(V600E) inhibitor PLX4720 blocked *in vivo* tumor growth in a xenograft mouse model. Thus, the common antiarthritis drug leflunomide may be most effective for melanoma treatment when combined with a BRAF(V600E) inhibitor. (*Nature* 471:518–22, 2011) *Selected by T. Schwarz*

TGFBR1 genotype–phenotype

Although a 4-Mb region of chromosome 9q22.3 was previously identified as the disease locus for multiple self-healing squamous epithelioma (MSSE), the causative gene remained elusive. Goudie and colleagues recently investigated the genetic basis of this autosomal dominant skin cancer condition using exon capture and high-throughput sequencing and identified independent mutations in the gene encoding the transforming growth factor-β receptor 1 (*TGFBR1*), which is actually outside the implicated genomic region, in three affected families. Sequencing of the exons in this gene revealed 11 mutations from 18 of the 22 available families affected with MSSE. These results highlight another link between *TGFBR1* and cancer, and, interestingly, the distinct spectrum of loss-of-function *TGFBR1* mutations in MSSE correlates with the distinct biphasic skin cancer phenotype as opposed to the *TGFBR1* mutations identified in Marfan syndrome–related disorders, which involve altered cardiovascular, neurocognitive, and craniofacial–skeletal development. (*Nat Genet* 43:365–9, 2011) *Selected by J. McGrath*

What's in the water?

Recently, epidemiological evidence and anecdotal accounts have suggested that increased water hardness is associated with increased eczema prevalence. Hard water may exacerbate eczema because of increases in soap and detergent use that may irritate dry skin, interactions between soap and calcium in the water, enhancement of allergen penetration due to skin barrier disruption, or increased bacterial colonization of the skin. To investigate the effects of ion-exchange water softener on the severity of eczema in children, the Softened Water Eczema Trial was commissioned in the United Kingdom. No benefit of ion-exchange water softener use in combination with usual care was found in children with eczema. Although three of the four patient-reported secondary outcomes exhibited a small but significant effect, these differences may have resulted from response bias. Thus, the results of this study do not support the use of ion-exchange water softeners for the treatment of moderate to severe eczema in children. (*PLoS Med* 8:e1000395, 2011) *Selected by P. Bergstresser*

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